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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/009,009	Applicant(s) BRAIN ET AL.	
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3 and 4* is/are allowed.

6)☒ Claim(s) *2 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an application filed on 12/20/01. There are eleven claims pending and eleven under consideration. Claims 1-4 and 8 are compound claims. Claim 11 is a composition claim. Claims 9 and 10 are use claims. Claims 5-7 are synthesis claims. This is the first action on the merits. The application concerns some carbonyl-piperidine and carbonyl-piperazine compounds, compositions, synthesis, and uses thereof.

Abstract

2. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 1, including the figure, and the utility.

Claim Objections

3. Objection is made to claim 8 under 37 CFR 1.75 as being a duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial

duplicate of the allowed claim. See MPEP § 706.03(k). The phrase "for use in treatment" is a statement of intent. This is a purely mental act with no physical consequences. Thus, claim 8 is a compound claim with the same limitations as claim 1.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are two dashes separated by a space in line 1 of the claim. What does Applicant intend by this? In line 2 of the claim, the species lacking the diphenylethylamino group begins with "-5". With no additional substituents on the benzoic acid phenyl ring, this is not possible because substituents would have to be numbered 2-4.

In the alternative, if the diphenylethylamino limitation is meant to apply also to the second species, the Examiner suggests adding the word prior to the "-5" referred to above.

5. Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between

the steps. See MPEP § 2172.01. The omitted steps are: the reagents and reaction conditions required to perform Applicants' claimed synthetic transformation. All the word "reacting" does is label those compounds that are starting materials and those compounds that are products. The word "reacting" does not convey to the average organic chemist what reactions are contemplated. An acid and amine will not alone react to form an amide. Pyrrolysis or additional condensing agents are required. This is shown in Streitwieser (Introduction to Organic Chemistry, 2nd Ed.) in the second and third paragraph on page 515.

Applicants' claim 5 uses the word "comprises". What has been omitted from the claim is the third reagent or the heat, which must be added to the reaction to cause the amide bond forming reaction to occur. It is certainly within the skill of the average organic chemist to experimentally determine the additional reagents and conditions are required. Thus, an enablement rejection is not appropriate.

Beyond the paragraph spanning pages 4 to 5 and the paragraph spanning pages 5 to 6, Applicants give no guidance as to how the "reacting" is to be performed. The paragraph spanning pages 4 to 5 simply repeats the claim language. The paragraph spanning pages 5 to 6 describes forming an acid chloride from the acid with the reagent thionyl chloride. An acid chloride is a different a different species than an acid. Thus, the paragraph spanning pages 5 to 6 provides

no guidance as to how to react an acid with an amine, only how to react an acid chloride with an amine. Addition of thionyl chloride to a mixture of an acid and an amine would, of course, be foolish. Thus, Applicants have no support in the specification for the addition of the additional condensing agent or for pyrrolysis.

The Examiner suggests claiming reaction of an acid chloride with an amine to produce compound IA, relying upon the paragraph spanning pages 5 to 6 for support.

6. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The symbols "(a)" etc. below the arrows in the scheme pictured in this claim are art-recognized in synthetic organic chemistry as indicative of the reagents, temperatures, solvents, and reagents required to effect the individual reactions shown. However, there is no indication in the claim what "(a)" etc. mean. In the first complete paragraph on page 16, Applicants indicate using open language, the reagents which may be used. The Examiner suggests replacing the abbreviations "(a)" etc. by these reagent formulas in the scheme or adding at the bottom of the scheme, what is meant by the abbreviations.

7. Claims 8 and 9 provides for the use of the compounds of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 8 and 9 are also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

8. Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a disease or condition in which bradykinin B_1 receptor activation plays a role or is implicated".

It is unclear what diseases and treatments Applicants are intending to encompass. In the penultimate paragraph on page 21 Applicants list, using open language, some bradykinin B_1 associated diseases. In the last paragraph on page

21, page 22, and the first three paragraphs on page 23, Applicants list a number of additional conditions they intend to treat. Are these also "a disease or condition in which bradykinin B_1 receptor activation plays a role or is implicated"? Reference to the IgE receptor would suggest that asthma is not such a condition but what about psoriasis and eczema? Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

The Examiner suggests using the specific diseases Applicants intend to treat using the passages cited above for support.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing pain, does not reasonably provide enablement for preventing all other claimed diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the carbonyl piperazine compounds such as present here. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. The Examiner suggests deletion of the word "prevention".

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the

predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. Determining if any particular claimed compound would prevent any particular disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with healthy volunteers to see if a disease could be prevented, a large degree of experimentation. The direction concerning the prevention of diseases is found in the last paragraph on page 24, which merely states Applicants' intention to do so. There is no working example of prevention. The state of the art is summarized by Marceau (Pharmacol Rev.) who states in the last complete sentence on page 19 that, "[p]ractically nothing is known about the clinical pharmacology of the B1R [the bradykinin B1 receptor]".

The artisan using Applicants invention would be a physician with a MD degree and several years of experience. The nature of the invention is clinical treatment of disease, which involves physiological activity. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The scope of the claims involves all of the thousands of compounds of formulas I and IA as well as the presently unknown list of diseases embraced by claim 9.

Allowable Subject Matter

10. Claims 1, 3, and 4 are allowed. Claim 2 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action. Claim 7 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Applicants claims are novel over Ferrari (Ref AA). The reference teaches synthesis and bradykinin receptor binding of compounds that are toluene, naphthalene, and quinoline sulfonamides, not the required X^2 group of Applicants' claims.

Conclusion

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
March 6, 2003